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09/732,411	12/07/2000	Samy Ashkar	CMZ-124CP	1508

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	17

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/732,411	ASHKAR, SAMY
Examiner	**Art Unit**
Maher M. Haddad	1644

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *2, 6, 9-10, 14 and 20-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 7-8, 11-13, 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Claims 1-29 are pending.

2. Applicant's election with traverse of Group XXXI, claims 1, 3-9 and 11-19 and the species wherein endothelial cells as target cell and titanium as the substrate, filed 9/18/02 is acknowledged.

Upon reconsideration Examiner has extended the search to cover macrophage and neutrophil as the target cell and a polyvinyl surface, a gel, collagen, hyaluronic acid and PGA as the substrate, claims 1, 3, 4, 5, 7-8, 11-13 and 15-19.

Applicant's traversal is on the grounds that the SEQ ID Nos overlap regarding the types of receptor(s) and/or cells that some of the peptides binds and the number of groups that the Applicant has been restricted to should be revised based upon the receptors and cellular structures to which claimed peptides bind. This is not found persuasive because the specific peptides differ with respect to their structure, physiochemical properties and function. In addition, the different peptides are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Therefore the methods of inhibiting adhesion comprising providing the target cell with the specific peptide are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 2, 6, 9-10, 14 and 20-29 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 3, 4, 5, 7-8, 11-13 and 15-19 are under examination as they read on a method of inhibiting adhesion of a target cell to a substrate comprising providding the target cell with the adhesion modulatory peptided associated substrate SEQ ID NO:15 (inhibits VLA-4 VCAM interaction) such that adhesion of the target cell to the substrate is inhibited wherein the target cell is endothelial cells, neutrophil and macrophage and wherein the substrate is titanium, a polyvinyl surface, a gel, collagen, hyaluronic acid and PGA.

5. The disclosure is objected to because the " Calls " in page 2, line 18 and the "myofiboblasts" in page 3, line 31 are misspelled. Correction is required.

6. Claim 15 is objected to because of the following informalities: "myofiboblast" is missspelled. Appropriate correction is required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1, 4-5, 7-8, 11-13 and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite in its recitation of "modulating" because it is ambiguous as to the direction (positive or negative) or degree of said modulating. It is noted that the specification page 2 line 31 and page 3 line1 1-2 defined modulating to include stimulating, promoting enhancing, decreasing or inhibiting. The definition is made in an open language term and hence would open "modulating" to other relative terms and parameters.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

10. Claims 1, 3-5, 7-8, 11-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting adhesion of a target cell to a substrate *in vitro*, comprising providing the target cell with the adhesion peptide SEQ ID NO: 1-15 and SDV associated substrate, wherein the target cell is an endothelial, a macrophage or neutrophil and the substrate is a polyvinyl surface, a gel, collagen, hyaluronic acid, titanium and PGA, does not reasonably provide **enablement** for a method of "modulating adhesion" of a target cell to a substrate comprising providing the target cell with any "adhesion modulatory peptide"-associated substrate such that adhesion of the target cell to the substrate is "modulated" in claim 1, wherein the adhesion modulatory peptide comprises any **peptide** which specifically inhibits adhesion of the target cell in claim 3, wherein the adhesion modulator peptide is any "endothelial cell adhesion modulator peptide" any "fibroblast adhesion modulatory peptide" or any "macrophage adhesion modulatory peptide" in clam 4, wherein the adhesion modulatory peptide is any "endothelial cell adhesion modulatory peptide" in claim 5, wherein the adhesion modulatory peptide is any "neutrophil adhesion modulatory peptide" or any "myofibroblast adhesion modulatory peptide" in claim 7, wherein the "adhesion modulatory molecule" inhibits binding of any "adhesion receptor predominantly" expressed by the target cell in claim 11, wherein the target cell is within a "subject" in claim 17, the method further comprising contacting the substrate with the adhesion modulatory peptide, forming the adhesion modulatory peptide-associated substrate prior to providing the cell with the substrate in claim 19. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Applicant has not provided sufficient biochemical information that distinctly identifies such "adhesion modulatory peptide", "endothelial cell adhesion modulator peptide" and "macrophage adhesion modulatory peptide" other than SEQ ID Nos:1-15 and SDV peptide. While any adhesion modulatory peptide may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any adhesion modulatory peptide that can be used to inhibit adhesion of a target cell to a substrate *in vitro*.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Applicant has not enabled structurally related and unrelated compounds comprising "any adhesion modulatory peptide" which would be expected to have difference in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any peptide, which inhibits any adhesion activity for the number of possibilities associated with the myriad of direct and indirect effects associated with various adhesion pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any " peptide" or "adhesion modulatory peptide" and still provide or maintain sufficient or the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The specification does not provide a sufficient enabling description of the claimed invention. A person of skill in the art is not enabled to make and us "adhesion modulatory peptide" as recited in the claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their therapeutic potential. A person of skill in the art could not predict which particular amino acid sequences of SEQ ID NO: 15 are essential and could be used in a method of inhibiting adhesion. It is not clear that the skilled artisan could predict the efficacy of the breadth to the "endothelial cell adhesion modulator peptide" and "macrophage adhesion modulatory peptide", encompassed by the claims. The term "comprises" in claim 8 is open-ended that would open SEQ ID NO: 15 to include additional amino acids on either or both of the N- or C- termini of VLEP sequence.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the method of inhibiting adhesion indices adhesion inhibitory peptide such as adhesion-based molecules can be species – and model-dependent, it is not clear that reliance on the peptide of SEQ ID NO: 15 that inhibits Vla-4/VCAM interaction (page 10, Table II of the instant specification) accurately reflects the relative efficacy of the claimed "functional inhibition" in a subject.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a peptide's amino acid sequence and still retain similar biological activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly in tolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to tits function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain function aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

In support, Kogan et al. ((J. Biol. Chem.,1995) disclose that single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion binding activity (see entire document, including the Discussion). On the basis of the disclosed apparent in vitro observation alone, applicant concludes that the scope of the peptides defined by sequences encompassed by the claimed invention can have biological activity to inhibit the adhesion of target cell to the substrate and be provided as pharmaceutical compositions to subjects including human to effectively inhibit adhesion.

peptide therapies are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e., such as proteolytic degradation, immunological inactivation or due to and inherently short half-life of the peptide; (2) the peptide may not reach the target area because, i.e., the peptide may not be able to cross the mucosal or the peptide may be adsorbed by fluids, cells and tissues where the peptide has no effect; and (3) other functional properties, known or unknown, may make the peptide unsuitable for in vivo therapeutic use,. i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992)

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 1, 3-5, 7-8, 11-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of inhibiting adhesion of a target cell to a substrate *in vitro*, comprising providing the target cell with the adhesion peptide SEQ ID NO: 1-15 and SDV associated substrate, wherein the target cell is an endothelial, a macrophage or neutrophil and the substrate is a polyvinyl surface, a gel, collagen, hyaluronic acid, titanium and PGA.

Applicant is not in possession of a method of "modulating adhesion" of a target cell to a substrate comprising providing the target cell with any "adhesion modulatory peptide"-associated substrate such that adhesion of the target cell to the substrate is "modulated" in claim 1, wherein the adhesion modulatory peptide comprises any peptide which specifically inhibits adhesion of the target cell in claim 3, wherein the adhesion modulator peptide is any "endothelial cell adhesion modulator peptide" any "fibroblast adhesion modulatory peptide" or any "macrophage adhesion modulatory peptide" in clam 4, wherein the adhesion modulatory peptide is any "endothelial cell adhesion modulatory peptide" in claim 5, wherein the adhesion modulatory peptide is any "neutrophil adhesion modulatory peptide" or any "myofibroblast adhesion modulatory peptide' in claim 7, wherein the "adhesion modulatory molecule" inhibits binding of any "adhesion receptor predominantly" expressed by the target cell in claim 11, wherein the target cell is within a "subject" in claim 17, the method further comprising contacting the substrate with the adhesion modulatory peptide, forming the adhesion modulatory peptide-associated substrate prior to providing the cell with the substrate in claim 19.

Applicant has disclosed only peptides of SEQ ID NO: 1-15 and SDV; therefore, the skilled artisan cannot envision all the contemplated peptide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus

(Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 4-5, 12, 13, 16, and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S Patent No. 5,330,911

The '911 patent teaches a method of modulating/enhancing adhesion of a target cell to a substrate, comprising providing the target cell with a peptide grafted surfaces or YIGSR-linked substrates such that the target cell to the substrate is attached, indicating that cellular adhesion on these substrates is governed primarily by cell receptor-ligand interactions (abstract and column 5, line 24-39 and column 30, lines 33-37 in particular), wherein the cell is endothelial cells (column 6, lines 6-7 in particular), wherein the substrate is titanium (column 46, lines 15-16 in particular). Further, the '911 patent teaches the pretreatment of surfaces with a peptide prior to providing the endothelial cells with the substrate (see patented claim 45 in particular) as recited in instant claim 19.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
November 18, 2002

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